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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/484,879	01/18/00	ALVAREZ	V

020583
PENNIE AND EDMONDS
1155 AVENUE OF THE AMERICAS
NEW YORK NY 10036-2711

HM12/1024

EXAMINER	
WESSENDORF, T	
ART UNIT	**PAPER NUMBER**
1627	4

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/484,879	Alvarez
Examiner	**Group Art Unit**
T. Wessendorf	1627

☒ Responsive to communication(s) filed on *8/30/00*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-45* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-45* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Applicants claim to the priority is confusing. The first sentence, page 1 of the specification claims priority to S.N. 08/310,192. However, the continuing application filed on 01/18/00 recites S.N. 09/273,685. Clarification and/or correction is required.

The use of the trademark e.g., TWEEN at page 41, line 26 has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Applicant is requested to check for other trademarks present in the specification.

The disclosure is objected to because of the following informalities:

A). The status of application Serial No. 127,351 at page 46, line 1 has not been updated.

B). The heading "Figure Legends" at page 10 is incorrect. It should be changed to --Brief Description of the Drawings---.

Further, the peptide sequences included in the drawings should have a Seq. Identifier Number corresponding to those in the Seq. Listing.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific substance of interest, ligand and/or library, does not reasonably provide enablement for the broadly claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The scope of enablement provided in the specification is not commensurate in scope with the claimed molecule of undefined structure obtained via the claimed method having numerous unidentified parameters such as the first or second library peptide structure, antibody and its binding partner, antigen. The scope entails too numerous variables for not a single defined

structure or parameter is recited. However, the specification merely discloses a single e.g., compound for each of a claimed variable or parameter. For example, the specification discloses a specific molecule, abtide obtained using a specific ligand, mab 7E11-C5, which specifically binds to the specific antigen, human prostate carcinoma LNCap xenograft tumors, by screening a random peptide library, TSAR. Other than the single embodied parameter, no antibody of other structure or nature has been taught, or described in the specification. One skilled in the art is left to speculate the different e.g., antibodies or peptide libraries that could be employed such that a molecule of interest is obtained exhibiting a desired result or activity. The specification, lacks not only direction but guidance, as by working example or reasonable assurance, that a molecule obtained by the recited process would be capable of achieving the compound' desired result. One is left to embark on its own experimentation as to how to proceed in determining which antibody, peptide libraries, or antigen would cooperatively function to achieve the desired molecule having the desired function. In an highly unpredictable art, as e.g., antibody, this is nearly an impossible task. As stated by Lenstra (J. of Immunological Methods), page 155, col. 1, the number of antigenic clones in the library depended on the antibody used for immunoscreening. And, mimotopes are constructed and selected by

satisfying the binding requirement of one particular antibody. Consequently, a mimotope may be a reconstruction of the antigenic surface that is biased by only one antibody rather than a realistic representation. Mimotopes from several sites (II and IV) are not recognized by mAbs specific for other epitopes within the same site. Note further Gallop's (Ref. AT) disclosure as to the criteria and constraints which must be imposed on the creation of libraries that is used for drug discovery. Also, see Lam et al (Nature). Also, note applicant's disclosure at page 6, lines 18-22 of the instant specification. Applicant states that "..screening of peptide libraries has generally been confined to the use of a restricted number of ligands...most commonly,the ligand has been an antibody..." [Ligand is but one of the numerous undefined parameters that is instantly claimed.] Furthermore, at pages 23-25, applicant continues "a peptide library is screened with a ligand that possesses a specific, ..complex, binding site of interest. Those peptides in the library that are specific binding partners of the ligand bind to the ligand are readily recoverable because of this specific binding...example ..an antibody, inherently possessing an antigen binding site....". The particular embodiments of the invention requires that epitope to which an antibody specifically binds is known, page 26, lines 13-15. Also, at e.g., page 33, line 8 through page 34, line 5 of the instant specification. Applicant

states that "..one important aspect of screening the libraries is that of elution... in terms of TSAR expression by phage...[or] any system where the random peptide is expressed on a surface fusion molecule. It is conceivable that the conditions that disrupt the peptide-target interactions during recovery of the phage are specific for every given peptide sequence from a plurality of proteins expressed on phage. For example, certain interactions my be disrupted by acid pH's but not by basic pH's and vice versa.... it may be desirable to test a variety of elution conditions (including but not limited to pH 2-3, pH 12-13, excess target in competition, detergents, mild protein denaturants, urea, varying temperatures, light, presence or absence of metal ions, chelators etc.) and compare the primary structure of the TSAR proteins express on the phage recovered for each set of conditions to determine the appropriate elution conditions for each ligand/TSAR combination. Some of these elution conditions may be incompatible with phage infection because they are bactericidal...the ability of different expressed proteins to be eluted under different conditions may not only be due to the denaturation of the specific peptide region involved in binding to the target but also may be due to conformational changes in the flanking regions. These flanking

sequence may also be denatured in combination with the actual binding sequence; these flanking regions may also change their secondary or tertiary structure in response to exposure to the elution conditions which in turn leads to the conformational deformation of the peptide responsible for binding to the target." (Emphasis added). Other factors that demonstrate the high unpredictable effect of the specificity binding of the target-ligand are the irrelevant regions of the first peptide that could be bound in the second screening step; binding that could result in the second peptide having a structure with different binding specificity from that of the original ligand, the differences in forms of library members, differences in complexity, biological expression of the different type of recombinant host, mode of expression etc. [Applicants' remarks at e.g., page 37 in S.N. 08/488,161.]

These numerous factors or problems are realities faced by one skilled in the art for the successful practice of the claimed invention without undue experimentation. The specification is therefore merely replete with general statements but the exemplification is directed to a single antibody, peptide library etc. While applicant is not required to provide working example(s) however, it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their

properties it must appear in an applicants' specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combinations included in the claims are capable of accomplishing the desired result. Ex parte Forman, 230 USPQ 546, BPAI, 1986.

There is no way of reliably forecasting the structure of the peptide that would mimic the ligand in function or activity given the infinite parameters such as the ligand, peptide libraries, substance of interest etc. as broadly claimed. Determination of the scope and content of applicant's claims places an undue burden on persons skilled in the art. There are too numerous variables to adjust, the number of possible molecules or peptides to design and especially assay becoming incalculable. This situation poses extraordinary difficulties to solve before a peptide of the desired activity could be obtained. Except with regard to subject matter commensurate in scope with applicants exemplified successes, the specification invites experimentation in the hope that a discovery will be realized. No meaningful conclusions can be drawn from the single example or little direction provided in the specification. Applicant's evidence must be commensurate in scope with the breath of the claims. Applicant's need not guarantee the success of the full scope of

the broad claims. Here, however, skilled artisans are provided with little assurance of success.

The specification further fails to teach how to use the claimed molecule as a therapeutic composition. There is no disclosure in the specification as to the therapeutic effect of any of the recited molecule.

Claims 1-45 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). Claims 1-2, for example, use several terms that appear to mean the same thing thus, producing confusion and ambiguity. For example, the first and second ligand which is a specific binding partner of the substance of interest appears to be the peptide as recited in the preamble. Further, it is not clear whether the compound which comprises the peptide obtained from the first random library includes other components besides the first peptide and how or whether the second peptide indeed binds to the substance of interest.

B). The claimed "substance of interest" (claim 1) or "antigen of interest" (claim 2) appears to connote a multitude of substances or antigens.

C). It is not clear, within the claimed context, in what aspects the first and second random peptide libraries are

different from each other. For example, what is the identifying characteristics of the substance of interest that would fingerprint it from the non-substance of interest?
Claims 3 and 4.

D). The recited antibody, 7E11-C5, is improper. It is suggested that applicant provides either the structure or the function of the antibody e.g., one that binds to tumor antigen.

E). Claim 13 does not substantially differ from claim 12. While claim 23 recites for a comprising language however, it appears that the peptide sequence of ID. No. 2 consists of only the amino acid residues as recited in claim 13.

F). The metes and bounds of the claimed "binding portion", e.g., claim 12; "plurality of molecules", claim 32; "peptide of length between 5 and 40 amino acids", e.g., claim 33 are indefinite. For example, it is not clear as to the minimum or maximum numbers of molecules that could be obtained from the screening of libraries.

G). Claim 20 recitation of a library of recombinant vectors that express a plurality of heterofunctional fusion proteins lack antecedent basis of support from the base claim 14 which recites a library of peptides. This claim appears to broaden the base claim. Furthermore, the recitation of an `unpredictable' nucleotides goes against the requirement of the law that the claims be definite.

H). Claim 25 is confusing since the method encompasses two method steps i.e., in vivo and in vitro.

I). Claim 33 is indefinite as to how the method can produced different peptide lengths.

J). The method of claim 35 is indefinite as to the image of an internal region of a subject that is obtained and an omnibus claim.

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 12-13, 31, 34 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims1 and 2 of prior U.S. Patent No. 5,885,577. This is a double patenting rejection.

The claimed molecule comprising of the recited sequences is identical to the molecule recited in the 5,885,577 Patent.

Claims 37-39, 41-42 are rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-5 of prior U.S. Patent No. 6,015,561. This is a double patenting rejection.

The claimed molecule comprising of the recited sequences is identical to the molecule recited in the 6,015,561 Patent.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-45 are rejected under 35 U.S.C. § 102(a) or 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over 5 U.S.C. § 103 as being unpatentable over Kay [WO 18318(a)(I) or U.S. 5,498,538(e)(II)].

Kay (I), e.g., par. bridging pp. 7-8 and page 73, lines 3-15; pp. 50-51; pp. 84-115, discloses a molecule obtained by a method of identifying a peptide which binds to a substance of interest comprising screening a first random peptide library with a ligand and identifying a peptide that specifically binds to said ligand and recites screening a second random peptide library with a compound comprising said first peptide to identify a peptide which binds to said compound. Kay describes peptide (immunogens) identified by a two step screening process by generating a first series of TSARs specific for a given cellular or viral macromolecule ligand and then developing a second series of TSARs that bind to the first TSARs i.e., the first TSAR is used as a ligand to identify the second series of TSARs. The second series of TSARs will mimic the initial cellular or viral macromolecule ligand site but will contain only relevant peptide binding sequences, eliminating irrelevant peptide sequences. The claimed amino acid sequences are inherently or obviously possessed by the prior art peptide or molecule since the same antibody and screening methods as recited similarly employed by

the prior art. The claimed antibodies peptides (abides, as coined by applicant) appear to be the same or similar to the prior art, absent a showing of unobvious differences. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that there is a difference between the antibodies peptide sequences i.e., that the claims are directed to new materials and that such a difference would have been considered unexpected by one of ordinary skill in the art, that is, the claimed subject matter, if new, is unobvious. In the absence of evidence to the contrary, the burden is upon the applicants to prove that the claimed antibodies are functionally different from those taught by the prior art and to establish patentable differences. See in re Best 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (BPAI 1989).

None of the references cited above is included in this Office action since they have been provided to applicants in the previous applications.

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1627.

Certain papers related to this application may be submitted to Art Unit 1627 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 O.G. 61 (November 16, 1993) and 1157 O.G. 94 (December 28, 1993)(see 37 C.F.R. 1.6(d)). The official fax telephone numbers of the Group are (703)308-7924. NOTE: If applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. Wessendorf whose telephone number is (703) 308-3967. The examiner can normally be reached on Mon. to Fri. from 8 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat Ph.D., can be reached on (703) 308-0570. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

T. Wessendorf

T. Wessendorf
Patent Examiner
Art Unit 1627
10/23/00